Implementing Six Sigma Tools to Reduce Formulation Errors in a Compounding Pharmacy

Elisha S. Jiménez Acosta
Master in Manufacturing Competitiveness
Advisor: María García Sandoval, Ph.D.
Industrial and Systems Engineering Department
Polytechnic University of Puerto Rico

***Abstract* —** *Formulation errors are medication errors that occur when a prescribed mixture is not performed as per the required medical order. Formulation errors in compounded total parenteral nutrition units represent an inherent risk to the safety of the intended patient. A 46.43% increase in the metrics incidence associated with formulation errors was identified in a patient-specific compounding pharmacy. This project aimed to comprehend the effects of implementing six sigma tools in the compounding pharmacy's order entry process by focusing on reducing the incidence of the metrics associated with formulation errors by 50%. By applying the DMAIC methodology, the incidence in the metrics of formulation errors has been reduced, thus reducing the number of formulation non-conformances and external complaints.*

Key Terms *— Compounding Pharmacy, Formulation Errors, Process Improvement, Six Sigma.*

INTRODUCTION

Patient-specific total parenteral nutrition (TPN) is a compounded mixture of dextrose, lipid emulsions, and amino acid solutions (vitamin, electrolyte, and mineral supplements). This nutritional supplement is administered intravenously to patients who cannot ingest food orally; often, adult and pediatric patients requiring this nutrition are in a fragile state of health [1]. Because of this, the compounding process must be performed under the strictest guidelines and with the highest quality to ensure patient safety. The World Health Association (WHO) defines *patient safety* as a healthcare discipline that focuses on reducing and preventing risks, errors, and harm that occur to patients while in healthcare [2].

One of the most common errors presented when compounding TPN units is formulation/medication errors. Medication errors are preventable events that could cause or lead to patient harm [3]. These errors can occur while choosing a medicine, interpreting, or writing the prescription, manufacturing the formulation (incorrect strength, contaminants, incorrect packaging), compounding the formulation (incorrect dose, incorrect drug, incorrect formulation), or administering the medication or therapy [4].

The compounding of TPN units is a complex process that involves many manual tasks. One of the most critical tasks during the compounding process is the order entry task, which requires transcribing a medical order to the system that will communicate with the compounder. This manual process has been identified as prone to human error, causing an inherent risk for formulation errors. By improving the quality and safety measures in healthcare processes, risks could be reduced, ensuring patient safety [5] and a high-quality product.

A high incidence of input critical incidents has been noted in the compounding pharmacy. *Input critical incidents* are a metric evaluated by the quality department that describes in-process incidents that, if not detected internally, will result in formulation errors (i.e., dosage errors, an incorrect ingredient added, missing ingredients). It has been identified that for Q3 2022, the amount of input critical incidents equaled 53, higher than the amount of 25 reported in Q2 2022. This design project aims to implement the six-sigma methodology to reduce the amount of input critical incidents, thus parallelly reducing the complaints and investigations raised because of formulation errors (incorrect doses, incorrect units, incorrect drug) during the data entry process by at least 50%.

METHODOLOGY

This design project aims to implement six sigma tools (the DMAIC method) in the order entry process of the compounding pharmacy, located in Guaynabo, Puerto Rico, to reduce in-process incidents that are likely to result in formulation errors. The DMAIC methodology proposes to define the area of opportunity, measure its performance, analyze the process, and identify root causes for variation or defects. Improve the process by addressing the identified root cause and control the improved process to correct any nonconformance before resulting in defects.

Define Phase

During this phase, a project charter was developed (Table 1) to establish the project's goals, scopes, and critical actions. The process workflow for the order entry and verification in the compounding pharmacy was performed to identify in-process opportunities.

Table 1
Project Charter

CURRENT SITUATION	PROJECT TITLE
• Increase of Input Critical Incidents for Q3 2022 (i.e., dosage errors, formulation errors, etc.) • Three (3) Nonconformances identified in Q3 related to formulation errors. • Medical orders must be reprocessed if identified with errors, compounding process is delayed.	Implementing Six Sigma Tools to Reduce Formulation Errors in a Compounding Pharmacy
PROJECT GOAL	**PROCESS SCOPE**
• Reduce by 50% the amount of input critical incidents during the order entry process. • Improve OJT Training for Data Entry, First Verification and Second Verification • Increase risk awareness	• Order Entry Process • First Verification Process • Second Verification Process
BARRIERS TO SUCCESS	**CRITICAL ACTION**
• Improvement of the order entry software • Clean and Clear Medical Orders	• Gemba Walk • Process Flow Chart • Fishbone Diagram

The scope established for this project is to improve the order process in the compounding pharmacy by (1) reducing the incidence of in-process errors that, if not identified, can result in a non-compliant TPN unit; (2) improving the current on-the-job training for these tasks; and (3) increasing the risk awareness during these tasks.

A Gemba Walk was performed to understand the workflow process (Figure 1). The order entry task takes place within an ISO 8 (standard 14644-1) controlled environment. The medical orders are received by email or fax from 8:00 am to 11:30 am by an assigned pharmacy technician. During the Gemba Walk, it was noted that multiple customers sent handwritten medical orders. Once the medical order is received, it is confirmed with the customer.

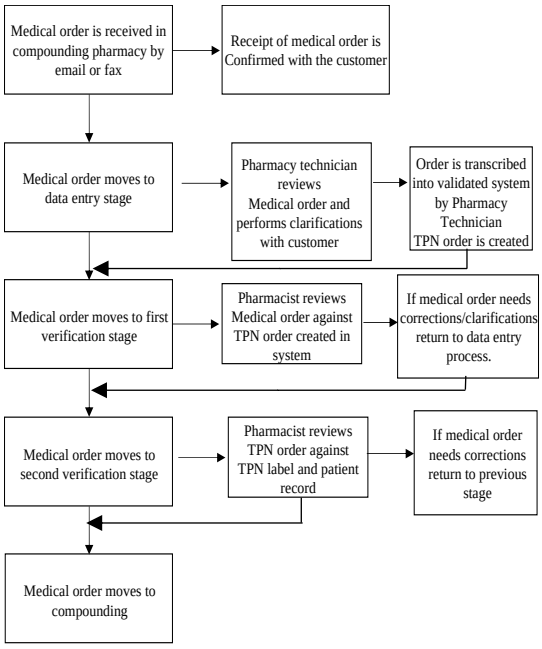

Figure 1
Order Entry Workflow Process

During the order (data) entry stage, a second pharmacy technician receives the created patient record with the medical order and, upon review, performs the required clarifications with the patient's doctor. Order is then transcribed into the validated system, thus creating the TPN order to be sent to the compounder. The medical order moves to the first verification stage.

During this stage, a licensed pharmacist verifies the transcribed TPN order against the physical medical order and patient record. This stage is the first checkpoint to identify input critical incidents (i.e., dosage errors, an incorrect ingredient added, missing ingredients). If no corrections or clarification are needed, the TPN label is printed, and the TPN order moves to the second verification process.

During the last verification process, a second licensed pharmacist performs an independent review of the TPN label and patient record. This stage is the last checkpoint to perform clarifications or corrections before sending the order to be compounded.

Several areas of opportunities were identified during this phase of the DMAIC:

- Personnel became distracted while performing the task.
- Personnel experienced fatigue due to high TPN volume.
- Pharmacists were seen multitasking.

Measure Phase

All the metrics related to formulation errors in the compounding pharmacy were evaluated to determine their likelihood of incidence. Measured metrics include but are not limited to Input-critical incidents, external complaints, and formulation non-conformance raised due to a non-compliant TPN unit being released to the customer. Incidents of input critical errors are parallel to the number of formulation errors detected internally. To correctly evaluate the tendency of the incidence of input critical errors, external complaints, and formulation non-conformances during Q2 2022 and Q3 2022 a frequency graph was performed (Figure 2). This frequency graph was performed with available data from Table 2.

Input critical errors were classified into three categories: (1) Incorrect dose errors, which result in the dose of one or more ingredients being higher or lower that the required dose; (2) Incorrect ingredients added, which is a result of one or more ingredient not required by the medical order being added, or the incorrect ingredient being selected in the TPN order; and (3) Order missing ingredients, which is a result of one or more ingredients required in the medical order not included in the TPN order (validated system).

Table 2
Tendency Evaluation: Metrics Related to Formulation Errors

Category		Q2 2022	Q3 2022
Input Critical Errors	Incorrect Dose	9	25
	Incorrect Ingredients Added	9	18
	Order Missing Ingredients	7	10
Formulation NCRs		1	3
External Complaints		0	0
Total		**26**	**56**

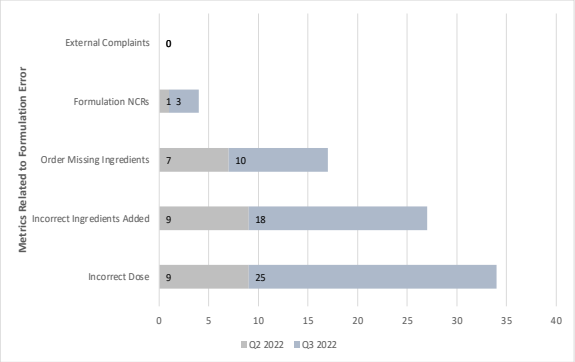

Figure 2
Tendency Evaluation: Metrics Related to Formulation Errors

The available data from Q2 2022 reported 25 input critical incidents, one formulation non-conformance, and zero external complaints due to formulation errors.

From the three categories of input critical incidents, the principal offender identified in Q2 2022 were incorrect doses and incorrect ingredients being added to the TPN unit. The formulation error non-conformance resulted from a TPN unit that was delivered to the patient with the incorrect dose of vitamin; this non-conformance was identified internally; thus, no external complaints were generated.

For Q3 2022 a 46.43% increase was identified in the quality metrics related to formulation errors.

Q3 2022 available data reported a total of 53 input critical incidents, three formulation nonconformances, and zero external complaints due to formulation errors. For Q3 2022 the major offender category for input critical was incorrect dose. Although the input critical incidents are captured internally, an adverse trend in this metric is a cause for concern. Formulation nonconformance rose from 1 to 3 in Q3 2022, meaning that the verification checkpoints in the process failed three independent times. Formulation non-conformances were found to be related to incorrect doses of ingredients being included in the TPN unit.

Analyze Phase

To analyze the contributing factors that lead to an adverse trend in the metrics related to formulation errors, an Ishikawa (fishbone diagram) was performed (Figure 3). With the development of this six-sigma tool, a general overview of all the involved factors was obtained.

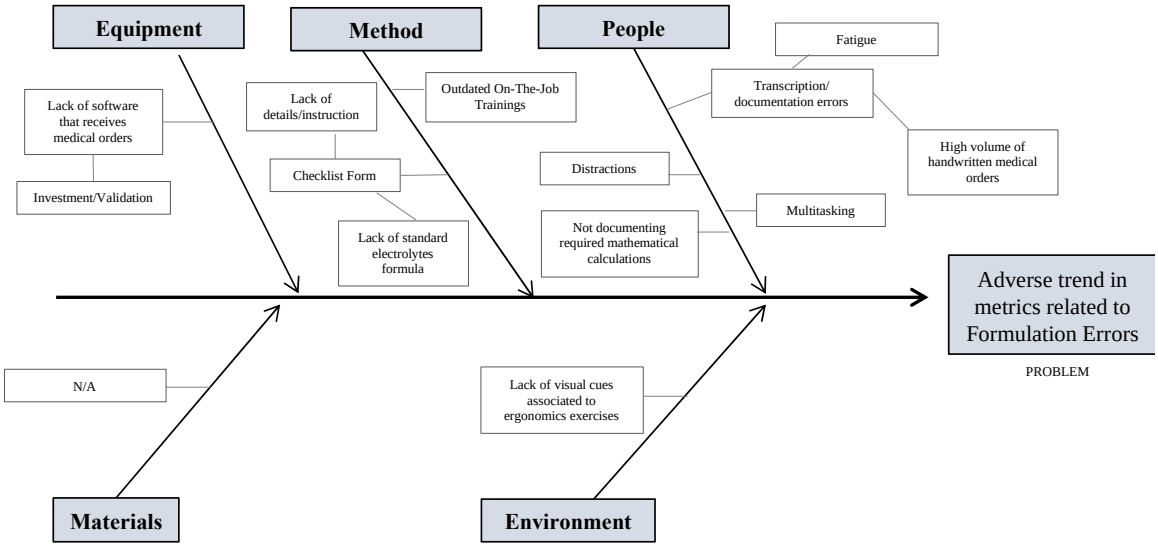

Figure 3
Ishikawa (fishbone) Diagram

Causes for the adverse trend in formulation metrics were identified in the fishbone diagram's people, environment, and method portion. Transcription/documentation errors were identified as the leading cause of input critical errors. Personnel was interviewed, and it was identified that these errors were more likely to occur when staff is fatigued. When personnel experiences fatigue, they may experience slower reactions, lack of awareness, and reduced capacity to analyze information, thus increasing the chances of errors [6].

Ergonomic exercises are in place to reduce eyestrain and fatigue. The order entry consists of spending revising medical orders and transcribing them to the validated system. The order entry stage was inspected, and it was identified that no visual cues were in place to remind personnel to perform ergonomic exercises.

One of the causes related to the adverse trend in metrics related to formulation errors was identified as outdated on-the-job training. It was identified that personnel with more than 10 years at the compounding pharmacy were not re-trained in the newer versions of the OJTs. This led to staff performing the same activities in a different manner. Local procedures and forms were reviewed in detail, and it was identified that the checklist forms for the verification process needed more details to successfully verify the order. The equipment portion of the Ishikawa diagram will not be considered under the improvement phase. Because acquiring software capable of communicating with customers to receive

medical orders electronically requires a substantial investment and a complete validation of the process, these actions should be considered for a future project.

Improvement Phase

Several corrective actions were implemented to reduce the number of formulation errors identified during the order entry stage. Visual cues were placed in the order entry area to mitigate the occurrence of fatigue in personnel. These visual cues consist of reminders to take eye breaks and stretches during the workday. The eye breaks shall follow the 20-20-20 rule, where personnel look away from the computer every 20 minutes for 20 seconds while focusing on objects 20 feet away. Ergonomic stretches shall be performed every three hours. The visual cues remind personnel of the frequency of performing eye rest and ergonomic exercises while performing the order entry and verification process.

Updating the on-the-job training to reflect the current process (per current procedure) of the order entry and verification process shall reduce the number of errors related to human factors (i.e., incorrect doses). All pharmacy staff must be re-trained by the quality staff in the new on-the-job and process procedure for the order entry, first verification, and second verification of the order.

The procedure was improved with the creation of a data entry checklist form. This checklist will provide pharmacy technicians with a physical copy of the performed task instructions to ensure that the process was performed according to the procedure; this form will be included in the patient record.

The verification checklist form was updated to include a section for Pharmacists to perform the manual calculations (e.g., standard electrolytes, dose calculations). The standard electrolytes formula shall be included in the revised verification form to simplify the calculation process and reduce the number of formulation errors, The re-training in the procedure and forms is expected to reduce the incidence of input critical errors (i.e., incorrect doses, incorrect ingredients added, omitted ingredients).

Control Phase

The effectiveness of the improvement phase and implemented corrective actions shall be measured in terms of the incidence of input critical errors and nonconformances related to formulation errors. For three months, the metrics related to formulation errors are expected to be reduced by at least fifty percent in the compounding pharmacy. To ensure the implemented actions are followed, prior to the release of the compounded TPN unit, the patient record is revised to ensure all proper documentation was completed and to verify the correct unit was compounded. Quality personnel also performs a quarterly inspection to ensure the compounding processes are performed per required SOPs.

RESULTS/DISCUSSION

Six Sigma methodology was implemented to efficiently identify all the assignable causes related to a high incidence of formulation errors in the compounding pharmacy. Several causes were identified, and corrective actions were implemented for Q4 2022. The placement of visual cues in the order entry area to remind pharmacy personnel of the frequency of eye breaks and ergonomic stretches, these visual cues have increased personnel participation in ergonomic exercises and consequently reduced the occurrence of fatigue in personnel.

On the other hand, re-training personnel on the updated on-the-job training, revised procedure, and forms has significantly reduced the number of input critical errors identified for Q4 2022.

A significant reduction in the metrics related to formulation errors has been identified upon implementing these corrective actions. To evaluate the metrics after the corrective actions were implemented in Q4 2022, a table was performed. Table 3 compares the available data from Q2, Q3 and Q4.

As identified in Table 3, the implemented actions reduced the metrics related to formulation errors in Q4 2022 by 64% compared to Q3 2022. Input critical errors were reduced significantly, and

no formulation nonconformances or deviations were identified in Q4 2022.

Table 3
Metrics Related to Formulation Errors After Corrective Actions

Category		Q2 2022	Q3 2022	Q4 2022
Input Critical Errors	Incorrect Dose	9	25	10
	Incorrect Ingredients Added	9	18	6
	Order Missing Ingredients	7	10	5
Formulation NCRs		1	3	0
External Complaints		0	0	0
Total		**26**	**56**	**21**

CONCLUSION

A high incidence in metrics related to formulation errors was observed in the compounding pharmacy for Q3 2022. In response to this, the order entry stage of the compounding process was studied, and corrective actions were implemented. This project aimed to reduce the incidence of metrics related to formulation errors by at least 50%. The Six Sigma methodology was executed during this project and helped identify several factors that led to a high incidence of in-process formulation errors. Corrective actions tailored to the leading causes for formulation errors were implemented for Q4 2022. The implemented actions effectively reduced the incidence of formulation errors (including in-process formulation errors) by 64%.

Further improvements were identified but were out of this project's scope; it is suggested that software capable of communicating with customers to receive medical orders electronically is implemented in the future. This software will reduce, in a more effective and controlled manner, the metrics related to input critical errors by eliminating handwritten medical orders.

REFERENCES

[1] E. Thomovsky, R. Backus, A. Reniker, F. A. Mann, and J. R. Dodam, "Parenteral Nutrition: Formulation, Monitoring, and Complications," *Contin Educ Vet.*, Vol. 29, No. 2: pp. 88-102, February 2007. Available: https://pubmed.ncbi.nlm.nih.gov/17727159/. [Accessed: October 2022].

[2] World Health Organization, "Patient Safety," *World Health Organization*, September 2019. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/patient-safety. [Accessed: October 2022].

[3] National Coordinating Council for Medication Error Reporting and Prevention, "About Medication Errors," *National Coordinating Council for Medication Error Reporting and Prevention* [Online]. Available: https://www.nccmerp.org/about-medication-errors. [Accessed: October 2022].

[4] J. Aronson, "Medication errors: what they are, how they happen, and how to avoid them," *QJ Med*, Vol. 102, No. 8, pp. 513-521, August 2009 [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/19458202/. [Accessed: October 2022].

[5] A. A. Kuwaiti, "Application of Six Sigma Methodology to Reduce Medication Errors in the Outpatient Pharmacy Unit: A Case Study from the King Fahd University Hospital, Saudi Arabia," *International Journal for Quality Research*, Vol. 10, No. 2, pp. 267-278, 2016. DOI:10.18421/IJQR10.02-03.

[6] Health and Safety Executive, "Human factors: Fatigue," Health and Safety Executive [Online]. Available: https://www.hse.gov.uk/humanfactors/topics/fatigue.htm. [Accessed: January 2022].